

State of the Art in Malignant Melanoma Therapy: Bench to Bedside

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10/11/14

15th Annual Advances in Oncology
October 10-11, 2014

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Disclosures

Ad Boards: OncoSec, NeoStem, Nektar, Prothena

The presentation will discuss but not endorse the use of investigational agents
and the possible use of drugs for as yet unapproved indications

Topics to cover—immuno

Bench

- ⊗ Interferons
- ⊗ Interleukin-2
- ⊗ CTLA4 blockade
- ⊗ PD-1, PD-L1 blockade
- ⊗ Tumor-infiltrating lymphocyte regimens
- ⊗ Lesional, local approaches

Bedside

- ⊗ Adjuvant>>advanced
- ⊗ Proof of principal but poor therapeutic index
- ⊗ Checkpoint blockers augment existing immune response
- ⊗ TIL cells exploit immune tumor microenvironment
- ⊗ Potent locoregional responses → systemic benefit

Topics to cover—molecular

Bench

- ⊗ Discovery of BRAF activating mutation in melanoma
- ⊗ Other oncogenic drivers, some in other tumors
- ⊗ Rapid emergence of resistance uncovered multiple new targets
- ⊗ Combinations appear promising therapeutically

Bedside

- ⊗ Rapid and dramatic responses to specific BRAF inhibitors
- ⊗ Equally dramatic emergence of resistance, sometimes mixed
- ⊗ Therapeutic index and drug interactions may limit combinations (like early ART)

Interferons—type I and II

Bench

- ⊗ IFN- α has pleiotropic immunomodulatory effects
- ⊗ Modest activity vs advanced melanoma but optimal with tumor burden ↓
- ⊗ Poorly-"customized" re: predictors of benefit/failure/tox
- ⊗ IFN- γ —narrower, different immunomodulatory effects but hard to harness therapeutically

Bedside

- ⊗ Widespread use in adjuvant Rx at high doses/long durations
- ⊗ Controversy remains re: risk and cost:benefit ratios
- ⊗ IFNs likely to be supplanted by narrower-activity cytokines in cancer

Interleukin-2

Bench

- ⊗ Murine data showed benefit dependent on dose, elaboration of LAK cells
- ⊗ Receptors related to other γ cytokines
- ⊗ Toxicities mediated by capillary leak, other cytokines
- ⊗ Mechanisms poorly-understood: increased AICD, Treg undesirable

Bedside

- ⊗ High doses required for clinical benefit=5-7% durable remission
- ⊗ Multi-organ toxicities life-threatening, limit access to selected pts, Rx centers
- ⊗ Predictive factors may be based on host, tumor factors (CWG "select")
- ⊗ Altered versions, enhancements and toxicity protectors all failed
- ⊗ Lower doses → T cell survival in adoptive T cell Rx

CTLA4 blockade

Bench

- CTLA4 competitively inhibits CD28:B7.1 binding after T cell activation
- Embryonic $-/-$ causes lethal lymphoproliferative syndrome
- Ab to CTLA4
 - Removes the inhibitory signal
 - Depletes Treg cells
 - Enhances melanoma-specific T cell motility

Bedside

- Fully-human CTLA4 Ab active in melanoma, sometimes with delayed response
- Autoimmunity in up to 30%
 - Colon
 - Skin
 - Pituitary
 - Liver
 - Others rarely
- Approved for advanced mcl, RFS benefit in adjuvant mcl

PD-1 axis blockade

Bench

- PD-1 mediates T cell exhaustion in viral, tumor immune responses
- Ligands—PD-L1, PD-L2
- PD-1 $-/-$ phenotype \rightarrow autoimmune, not lymphoproliferative
- Blockade on either side reverses exhaustion

Bedside

- Phase I studies showed early, marked regression in 30-40% of patients
- Several human or humanized Abs studied, 2 approved 2014
 - Nivolumab in Japan
 - Pembrolizumab in U.S. (accelerated, 2nd/3rd line)
- Ph IIIs test benefit of PD-1 and/or combined PD-1/CTLA4 block
- Will PD-1 or PD-L1 block or combination with ipi "win"?

Other immunotherapy combinations

Bench (or early trials)

- Inhibitors of negative regulators in tumor microenvironment
 - IDO inhibitor of MDSC
 - PLX3397 inhibitor of RTKs in tumor macrophages
- Immune costimulation
 - 4-1BB-Ab, CD40L, OX40-Ab
 - GM-CSF with ipilimumab
- Vaccines?

Bedside (later trials)

- CTLA4 +/- bevacizumab
- Other γ c cytokines, e.g. IL15 + PD-1 blk
- CTLA4-4 Ab plus radiotherapy
- Enhancers of ADCC
- Lesional, regional delivery
 - Viral \rightarrow imm'mod genes
 - Cytokines, DC activators

Tumor-infiltrating Lymphocytes

Bench

- Adoptive/autologous immune cell Rx melanoma \gg others
 - Lymphodepletion required
 - T cell expansion and survival are critical
 - Exploration of antigens \rightarrow individual tumor mutations
 - ?Role of tumor manipulations
 - Systemic Rx incl targeted
 - Radiotherapy to tumor
 - ?Other predictors "necessary and sufficient" for curative outcomes

Bedside

- Requirements daunting
 - Tumor accessible
 - Yield of TIL culture
 - ?tumor-specificity
 - Pt who can tolerate lymphodepletion, HDIL-2
- Outcomes encouraging in pts who get all components
 - ORR in 60-70% range
 - CRR in 15-20% range
 - PFS plateau?

Molecularly-targeted Rx

Bench

- BRAF activating mutations in $>50\%$ melanoma
 - Single site in 80%
 - Ras-independent activation
 - Transforming*
- N-Ras mutations (several sites) in 15-20%, nearly always exclusive of BRAF mut
- Other drivers include CDK, NF1, c-kit, GNA, fusion genes

Bedside

- First generation of inhibitors "dirty" \rightarrow occasional response
- Early trials in unselected pts failed to improve cytotoxic Rx
- BRAF assays came with selective BRAF inhibitors
 - Dramatic responses if mut+
 - Rapid emergence of resistance

Resistance to targeted Rx

Bench

- Vertical (add MEK inhibitor) and horizontal (inhibit AKT/PI3K path) promising
- Rapid discovery of multiple resistance mech's \rightarrow new drug targets, heterogeneity
 - CDK 4/6
 - Met
- Metabolic shifts, feedback loops and altered addictions

Bedside

- MEK inhibitors highly active as single agents in BRAF, not NRAS mutant
- Combined BRAF+MEK inhibition adds benefit
- Horizontal blockade strategies under investigation
- Therapeutic index likely to become unfavorable

Combination immuno+targeted

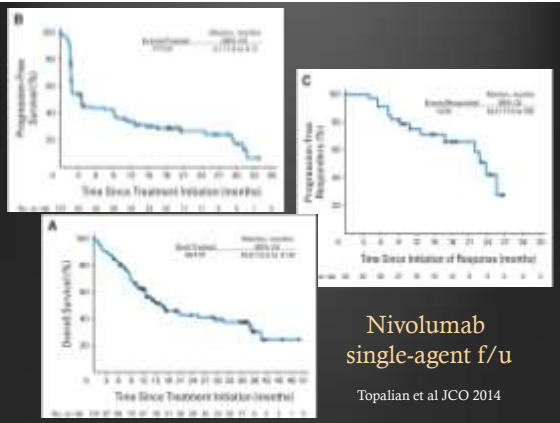
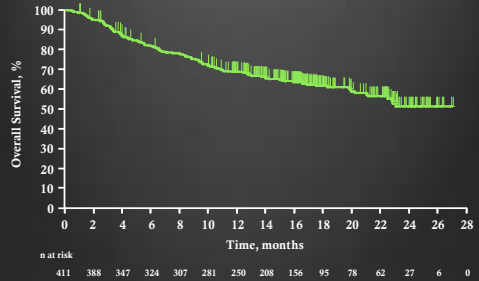
Bench

- ⊕ BRAF inhibition enhances immune functions to control melanoma
 - ⊕ T cell activity
 - ⊕ MHC expression
 - ⊕ PD-L1 ??
- ⊕ MEK inhibition inhibits T cells—the drugs are not mutation/activation-specific because MEK is upstream-activated

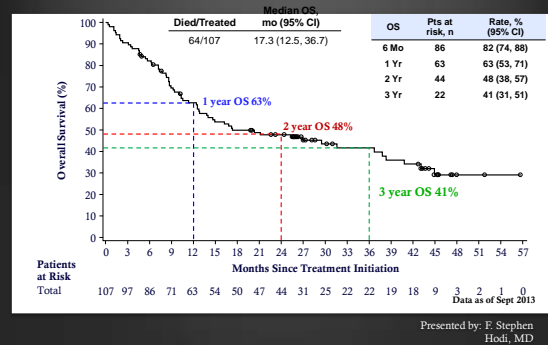
Bedside

- ⊕ Ipilimumab plus vemurafenib caused hepatotoxicity
- ⊕ PD-1 blockade plus targeted agents may be more tolerable

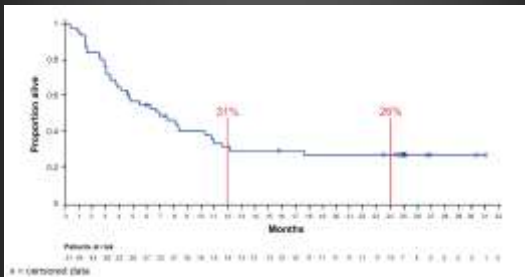
Pembrolizumab single agent data in advanced melanoma (Ribas et al ASCO 2014)



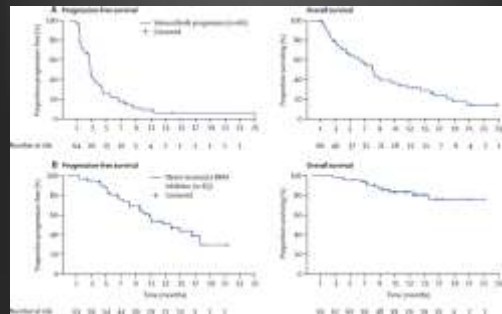
Survival for adv melanoma on nivolumab



Survival of melanoma pts with brain mets Rx'd with ipilimumab



Vemurafenib + cobimetinib (Ribas et al Lancet O, 2014)



The world is moving fast!

Melanoma

